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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,554	01/14/2004	Christine Lindsay Mummery	17360	5975

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,554	MUMMERY, CHRISTINE LINDSAY	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-132* is/are pending in the application.

4a) Of the above claim(s) *66,67,72-86 and 92-132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-65,68-71 and 87-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/31/05;1/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 45-132 are pending.

Election/Restrictions

Applicant's election with traverse of Group VI, claims 56 and 62 in the reply filed on 2/12/07 is acknowledged. The traversal is on the ground(s) that the Examiner's authority to require restriction is defined and limited by the statute 35 USC & 121 and the implementing regulation of USPTO is appropriate only in cases presenting inventions, which are both independent and distinct. Applicants argue that at least within the first category, Groups I-XXX are all related to each other and linked together under a single inventive concept and therefore are not independent and distinct. This argument is not persuasive because the inventions of the groups I-XXX are distinct each from the other because they are drawn to methods that have distinct steps, require separate compositions for practice and produce different product or results. For example, the steps of for causing non-spontaneous and controlled differentiation of an undifferentiated stem cell into a skeletal muscle cell or lineage from an embryonic stem cell cannot be used in a hematopoietic stem cell. Therefore, the inventions of the groups I-XXX are patentably distinct each from the other and will require separate and non-coextensive searches in the patent and non-patent literature. Applicant argue in view of the continued increase of official fees and potential limitations of the Applicant's financial resources a practice which arbitrarily imposes restriction requirements may become prohibitive and thereby contravene the constitutional purpose to promote and encourage the progress of science and useful arts. The restriction election requirement is not based on the financial resources of the Applicant but

on the patentably distinct groups, which require separate and non-coextensive searches in the patent and non-patent literature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 66-67, 72-86, 92-132 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/12/07

Claims 45-63, 65, 68-71, 87-91 are under consideration.

Claim Objections

Claims **68, 69, 90, 91** are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim is depended on a non-elected claim. See MPEP § 608.01(n). Accordingly, the claims **68, 69, 90, 91** have not been further treated on the merits.

Claim 68 is depended on non-elected claim 67.

Claim 69 is depended on claim 68, which is not under consideration.

Claim 90 is depended on non-elected claim 66.

Claim 91 is depended on non-elected claim 67.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims **45-47, 56-58, 62-64, 71, 87-88,** are rejected under 35 U.S.C. 102(b) as being anticipated by **Wobus et al**, (Roux's Arch Dev Biol, 204: 36-45, 1994).

Wobus et al, teach a method for controlling the differentiation of the D3 mouse embryonic stem cells into cardiomyocytes depending on the concentration and treatment time of retinoic acid (RA), where RA mimic endogenous signals involved in the differentiation (p 37, 1st and 2nd column) (**claims 45**).

Wobus teaches obtaining a cell population comprising a sub-population of differentiated cells of a mesodermal lineage by causing differentiation of the undifferentiated D3 stem cells with RA (**claim 46**).

Wobus teaches the differentiation signal is applied by culturing the undifferentiating D3 stem cells in the presence of RA influencing factor that induces differentiation of D3 stem cells into cardiomyocytes (**claim 47**).

Wobus teaches the in vitro differentiation of mouse D3 pluripotent ES cells (**claims 56-58**).

Wobus teaches the mouse D3 ES cells differentiate into a muscle cell, wherein the muscle cell is a cardiomyocyte and wherein the sub-population consists essentially of cardiomyocytes, about 10% of embryoid bodies treated with RA developed into cardiomyocytes (**claims 62-64, 71, 88**).

Therefore, Wobus clearly anticipates the claims.

Claims **45-46, 70, 87** are rejected under 35 U.S.C. 102(b) as being anticipated by **Wobus et al**, (J Mol Cell Cardiol, 29: 1525-1539, 1997).

Wobus et al, culture and transfection of the mouse embryonic stem cell line D3 cultivated in undifferentiated state on feeder layer of primary mouse embryonic fibroblasts and

their differentiation into cardiomyocytes after RA treatment (p 1526-1527, under materials and methods) (**Claims 45-46, 70**).

Wobus teaches single cardiomyocytes from 7+8 day old embryoid bodies were isolated (p 1529, 2nd column, under preparation of cardiomyocytes for electrophysiological measurements) (**claim 87**).

Therefore, Wobus clearly anticipates the claims.

Claims **45-51, 53-54, 60-63,** are rejected under 35 U.S.C. 102(b) as being anticipated by **Mummery et al**, (Differentiation, 46: 51-60, 1991).

Mummery et al, teach when P19 embryonal carcinoma (EC) cells were co-cultured with cells from one of several established visceral-endoderm-like cell lines, the EC cells were rapidly induced to aggregate and differentiate into cell types including mesoderm-derived cardiac and skeletal muscle (p 53, under methods, and abstract) (**claims 45-46**).

Mummery et al, teaches a differentiation-inducing factor secreted by END-2 cells wherein the visceral-endoderm-like cells indeed secrete differentiation-inducing activity for P19 embryonal carcinoma cells, where the medium was conditioned by confluent cultures of END-2 cells for 3 days (p 56, 2nd column; p 57; and materials and methods) (**claims 47-51, 53-54**).

Mummery et al, teaches that in order to establish whether direct contact between the feeder layers and P19 EC cells was necessary to induce differentiation in co-culture, the END-2 cells were plated in petri dishes, covered with soft agar and suspensions of P19 EC cells inoculated above the agar and after pre-culturing the formed aggregates were plated on gelatin coated flasks after 4 days and scored for areas of beating muscle 18 days alter (p 55, 2nd column under the role of cell contact in EC cell differentiation) (**claims 60-63**).

Therefore, Mummery clearly anticipates the claims.

Claims **45-46, 59** are rejected under 35 U.S.C. 102(b) as being anticipated by **Gearhart et al,** (WO 98/43679; 08.10.98).

Gearhart et al, teaches collection of human primordial germ cells (PGC) and derivation of embryonic germ cells derived from human aborted fetal material (p 41, lines 15-25, example 1). Gearhart teaches the human PGC and STO mouse fibroblasts were cultured; passage of pluripotent cells and isolation of human embryonic germ cells and human EG-derived cardiomyocytes are generated (p 28-29 and example 2). Gearhart et al, teaches the EG cells are maintained in the undifferentiated stage by culture on primary embryonic fibroblasts and to induce cardiomyocyte differentiation EG cells are detached from feeder layer and plated on in typical EG medium with LIF and EG derived cardiomyocytes can be further purified by the use of cardiomyocyte specific promoters driving a selectable marker, e.g., the alpha-cardiac myosin heavy chain (MHC) promoter fused to the neomycin resistance gene (p 29).

Therefore, Gearhart clearly anticipates the claims.

Claim 90 is rejected under 35 U.S.C. 102(b) as being anticipated by **Rohwedel et al**, (Dev Biol, 164(1): 87-101, 1994).

Rohwedel teaches a skeletal muscle cell by culturing embryonic stem cells after applying external signals (abstract).

Thus, **Rohwedel** anticipates the claim.

Claim 91 is rejected under 35 U.S.C. 102(b) as being anticipated by **Mummery et al**, (Differentiation, 46: 51-60, 1991).

Mummery teaches a vascular endothelial cell (throughout the document).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 55, 65, 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mummery et al**, (Differentiation, 46: 51-60, 1991) in view of **Mummery et al,** (Biochem Biophys Res Commun, 191(1): 188-195, 1993).

Mummery et al, teach when P19 embryonal carcinoma (EC) cells were co-cultured with cells from one of several established visceral-endoderm-like cell lines, the EC cells were rapidly induced to aggregate and differentiate into cell types including mesoderm-derived cardiac and skeletal muscle (p 53, under methods, and abstract) (**claims 45-46**).

Mummery et al, teaches a differentiation-inducing factor secreted by END-2 cells wherein the visceral-endoderm-like cells indeed secrete differentiation-inducing activity for P19 embryonal carcinoma cells, where the medium was conditioned by confluent cultures of END-2 cells for 3 days (p 56, 2nd column; p 57; and materials and methods) (**claims 47-51, 53-54**).

Mummery et al, teaches that in order to establish whether direct contact between the feeder layers and P19 EC cells was necessary to induce differentiation in co-culture, the END-2 cells were plated in petri dishes, covered with soft agar and suspensions of P19 EC cells inoculated above the agar and after pre-culturing the formed aggregates were plated on gelatin coated flasks after 4 days and scored for areas of beating muscle 18 days alter (p 55, 2nd column under the role of cell contact in EC cell differentiation) (**claims 60-63**). Mummery also

teaches that in murine embryogenesis mesoderm is formed on about 7 day 7 p.c. from embryonic ectoderm in a specific area adjacent to viscera endoderm (p 59, 1st column). Mummery notes the mechanism in mesoderm formation and the nature of the inducing signals is however, yet unknown (p 59, 1st column). Mummery differs from the claimed invention by not teaching a human stem cell differentiating into a cardiomyocyte.

However, at the time the claimed invention was made, **Mummery et al,** (Biochem Biophys Res Commun, 191(1): 188-195, 1993) teach that the differentiation of blastocyst stage mouse embryonic stem cells in culture is regulated by the fibroblast growth factor and its receptor (throughout the document). Mummery also teaches that FGF-receptor isoforms are also expressed on the human embryonal carcinoma, which are undifferentiated stem cells of human teratocarcinomas similar to the blastocyst stage mouse embryonic stem cells. Mummery also teaches in contrast to murine cell lines human EC cells express in addition to FGF receptors several other classes of growth factor receptors such as TGF beta, IGF, EGF which are factors involved in autocrine growth factor regulation. Mummery suggests since all these factors are expressed by the undifferentiated cells in both human and mouse embryonic stem cells these cells provide a useful model to study changes in the FGF-mediated signal transduction pathways during differentiation (p 194). As such, **Mummery et al,** (Biochem Biophys Res Commun, 191(1): 188-195, 1993) provide sufficient motivation for one of ordinary skill in the art to apply the mouse culture system of **Mummery et al**, (Differentiation, 46: 51-60, 1991) for study of signal transduction pathways in the human EC cells.

Accordingly, in view of the teachings of **Mummery et al,** (Biochem Biophys Res Commun, 191(1): 188-195, 1993) it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the mouse system to a human system with a reasonable expectation of success. One of ordinary skill in the art would have been

sufficiently motivated to make such a modification as Mummery in the mouse system taught in murine embryogenesis the mechanism of mesoderm formation is yet unknown **Mummery et al**, (Differentiation, 46: 51-60, 1991) and the human system may be a potential target for FGFs in the developing embryo **Mummery et al,** (Biochem Biophys Res Commun, 191(1): 188-195, 1993) (p 194).

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

At the time of the instant invention, claims 52, 68 and 69 were free of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 45-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 of U.S. Patent No. U.S. 11/644,790. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims embrace differentiation of undifferentiating stem cells after treatment with a differentiation signal.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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